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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/897,107	07/03/2001	Akihiko Yamagishi	210383US0	9251

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[REDACTED] EXAMINER

RAMIREZ, DELIA M

ART UNIT	PAPER NUMBER
1652	(7)

DATE MAILED: 08/26/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/897,107	YAMAGISHI, AKIHIKO	
	Examiner	Art Unit	
	Delia M. Ramirez	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 18 June 2003.
- 2a) This action is **FINAL**. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 17-26 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 17-26 is/are rejected.
- 7) Claim(s) _____ is/are objected to.
- 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) The proposed drawing correction filed on _____ is: a) approved b) disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) All b) Some * c) None of:
1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) The translation of the foreign language provisional application has been received.
- 15) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Status of the Application

Claims 17-26 are pending.

Applicant's cancellation of claims 1-16 and addition of claims 17-26 in Paper No. 16, filed on 6/18/2003 is acknowledged.

Applicant's submission of a declaration under 37 CFR 1.132 by Akihiko Yamagishi in Paper No. 15, filed on 6/18/2003 is acknowledged.

Applicants have submitted a request for priority in Paper No. 14, filed on 6/18/2003 under 35 USC 119(a)-(d) to JAPAN 2000-201920 and JAPAN 2001-164332. It is noted however that foreign priority claims to such applications have already being acknowledged by the Examiner in previous Office Action Paper No. 12, as indicated in page 3, paragraph 2 of the action. Copies of these foreign documents have been placed of record in the file.

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Specification

1. The abstract of the disclosure is objected to for not complying with the proper language and format. The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details. The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc. Correction is required. See MPEP § 608.01(b).
2. The amendment filed on 6/18/2003 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the

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disclosure of the invention. The added material which is not supported by the original disclosure is as follows: in page 2, lines 25-26, Applicants have amended the specification to read "amino acid sequences of proteins belonging to the same family". The Examiner has not been able to locate support of "proteins belonging to the same family". As such, Applicant is required to cancel the new matter in the reply to this Office Action.

Drawings

3. The drawings are objected to for not complying with sequence rules. See for example, Figures 2, 6-7 and 9. Applicant is required to insert sequence identifiers in front of the sequences depicted in the drawings or identify the sequences depicted in the drawings by using the corresponding sequence identifiers in the Brief Description of the Drawings. See 37 CFR 1.821(d). Appropriate correction is required.

Claim Objections

4. Claims 17 and 23 are objected to because of the following informalities: for clarity, it is suggested that the term "and replacing one or more amino acid residues of the protein different from those of the ancestral protein with the same amino acid residues as those of the ancestral protein" be replaced with "and replacing one or more amino acid residues which are different from those of the ancestral protein with the same amino acid residues present in the ancestral protein at those positions" or similar. Appropriate correction is required.

5. Claims 18 and 24 are objected to because of the following informalities: for clarity, it is suggested that the term "thermostability of protein according to claim #" be replaced with "thermostability of a protein according to claim #". Appropriate correction is required.

Claim Rejections - 35 USC § 112, Second Paragraph

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 17-26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

8. Claims 17 and 23 (claims 18-22 and 24-26 dependent thereon) are indefinite in the recitation of "proteins belonging to the same family" as it is unclear in the absence of a statement indicating the characteristics which are encompassed by the term "same family". As written, it is unclear if the proteins are structurally related, functionally related or both. For examination purposes, it will be assumed that the term refers to proteins which have similar structure and/or function. Correction is required.

9. Claims 17 and 23 (claims 18-22 and 24-26 dependent thereon) are indefinite in the recitation of "wherein said proteins evolutionarily correspond to each other in a phylogenetic tree" as it is unclear what the meaning of the term as recited in the claims and the specification provides no clue as to the meaning of the term. As such, one cannot determine how the term further limits the proteins to be compared. As written, it is unclear if the term refers to (1) proteins which have similar biological function, similar structure, or both, and (2) whether or not the term is also limiting the organisms from which such proteins are isolated based on their position in a phylogenetic tree. For examination purposes, no patentable weight will be given to the term, therefore the claims will be interpreted as a method for improving thermostability of proteins which comprises comparing the amino acid sequences (by multiple alignment in the case of claim 23) of proteins isolated from two or more species wherein the proteins have similar structure and/or function, and further comprises steps (ii), (iii), (iv) and (v) as recited in the claims. Correction is required.

Claim Rejections - 35 USC § 112, First Paragraph

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 17-26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claims 17-26 as amended are now directed to a method for improving thermostability of proteins which comprises comparing amino acid sequences belonging to the same family and deriving from two or more species, wherein said proteins evolutionarily correspond to each other in a phylogenetic tree. The claims are now drawn to a method which compares a genus of amino acid sequences for which there is no support in the specification as originally filed. See also discussion above in regard to the term "same family". Thus, there is no indication that methods for improving thermostability of proteins as recited were within the scope of the invention as conceived by Applicants at the time the application was filed. Accordingly, Applicants are required to cancel the new matter in response to this Office Action.

12. Claims 17-26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

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13. This rejection, which was discussed at length in Paper No. 12, mailed on 12/18/2002, was applied to canceled claims 1-6 and 11-16 and is now applied to newly added claims 17-26 for the reasons of record and the reasons set forth below.

14. Applicants argue that Applicants have rewritten claims 1 and 2 as new claims 17 and 23, respectively, to clearly indicate that the amino acid sequences compared belong to proteins of the same family. Furthermore, Applicants assert that the claims have been amended to include steps (iv) and (v) for completeness. Applicants also argue that the application provides information in regard to amino acid sequences of proteins which correspond to each other and assert that one of skill in the art would know that proteins which are derived from two or more species correspond to each other when these proteins appear at the similar location in the phylogenetic tree designed for each individual species.

15. Applicant's arguments have been fully considered but are not deemed persuasive to avoid the rejection in regard to newly added claims 17-26. While Applicant's amendments to the claims are acknowledged, it is noted that claims 17-26 as written, are still directed to a method for improving thermostability by comparing the amino acid sequence of proteins of different function. See claim interpretation above in claim rejections under 35 USC 112, second paragraph. Even if one assumes that the intended meaning of the term "proteins of the same family" is "proteins of similar function", it is noted that the scope of the claims is such that it encompasses improving the thermostability of any protein of any function. Therefore, to adequately described the claimed method, one of skill in the art would require disclosure of the amino acid sequences of those functional homologs which are required to construct the ancestral protein. Furthermore, since the method requires comparison of protein sequences of any species, one would require disclosure of those proteins (i.e. function) which can have their thermal stability enhanced. It is noted that while one would expect most proteins of diverse function from thermophilic bacterial to be thermally stable, this may not be the case for proteins of any function from non-thermophilic organisms. Therefore, it is expected that only those proteins which have similar

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function in thermophilic organisms and non-thermophilic organisms may have their thermal stability enhanced. In regard to arguments that one of skill in the art would know that proteins derived from two or more species correspond to each other when these proteins appear at the similar location in the phylogenetic tree designed for each individual species, it is noted that while one could have a phylogenetic tree specific to an individual protein type, it is unclear as to how one could have a phylogenetic tree specific to an individual organism (i.e. species) since, as known in the art, branches in phylogenetic trees correspond to organisms. Therefore, for the reasons set forth above and those already discussed in previous Paper No. 12, one cannot reasonably conclude that the claimed invention is adequately described.

16. Claims 17-26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for improving the thermostability of 3-isopropylmalate dehydrogenases wherein amino acid sequences of 3-isopropyl malate dehydrogenases and isocitrate dehydrogenases are compared, does not reasonably provide enablement for a method for improving thermostability of (1) any protein wherein the amino acid sequences of proteins of different functions are compared or (2) any protein of any function. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

17. This rejection, which was discussed in previous Paper No. 12, mailed on 12/18/2002, was applied to canceled claims 1-6 and 11-16 and is now applied to new claims 17-26 for the reasons of record and the reasons set forth below.

18. Applicants argue that the specification discloses the present invention in generic terms and provides a practical example which shows how to make and use the invention in agreement with the scope of what is being claimed. Applicants also argue that the Examiner has question the limited number of examples drawn to distinct proteins. Therefore, Applicants submit that the specification (pages 2-3)

teaches that (1) the method claimed is independent of the particular properties of the proteins used, (2) the method is based on the concept that ancestors common to eubacteria, eukaryotes and archaebacteria might be ultra-thermophilic based on the location of these organisms in a 16S rRNA based phylogenetic tree, and (3) in the design of a thermostable protein , it is more important that an ancestral protein be estimated. In support of Applicant's arguments, a declaration by Akihiko Yamagishi has been submitted, in which the thermostability of a glycyl tRNA was improved using a phylogenetic tree and estimating an ancestral protein. In view of the arguments and evidence presented, Applicants request withdrawal of the rejection.

19. Applicant's arguments have been fully considered but are not deemed persuasive to avoid the rejection of newly added claims 17-26. As indicated above, claims 17-26 as written, are still directed to a method for improving thermostability by comparing the amino acid sequence of proteins of different function. See claim interpretation above in claim rejections under 35 USC 112, second paragraph. Even if one assumes the meaning of the term "proteins of the same family" as "proteins having similar function", the arguments and evidence presented are not found persuasive for the following reasons. While the Examiner acknowledges the teachings of the specification (pages 2-3) and Applicant's declaration in support of the argument that the claimed method can be practiced to improve the thermostability of any protein, it is noted that in the example provided in the specification and that of the declaration, construction of the phylogenetic tree and the ancestral protein required the use of proteins from thermophilic bacteria which have functional homologs in non-thermophilic organisms. Therefore, in both cases, the proteins which had their thermostability enhanced were proteins which had functional homologs in thermophilic organisms. It is also noted that limitations in regard to the use of proteins from thermophilic organisms in the construction of the ancestral protein are not currently recited in claims 17 and 23. Furthermore, as indicated in the example provided in the specification and the declaration presented, the amino acid sequences used in the construction of the phylogenetic tree and the ancestral protein were known in the prior art. Therefore, since the scope of the claims encompasses enhancing the

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thermostability of any protein, it is unclear as to how one can practice the claimed method using amino acid sequences which are unknown in the art and are not disclosed in the specification. As discussed at length in Paper No. 12, while one could argue that the amino acid sequences required to practice the claimed method can be isolated by sequence comparison with structures disclosed in the prior art, isolating functional homologs based on structural homology is unpredictable as evidenced by Bork, Broun et al., Seffernick et al. and Van de Loo et al. previously discussed. In view of the information provided, the teachings of the art in regard to the unpredictability of isolating functional homologs based on structural homology, and the lack of knowledge as to which proteins can have their thermal stability enhanced, one cannot reasonably conclude that the specification is fully enabling for the full scope of the claims.

Claim Rejections - 35 USC § 102

20. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

21. Claims 17 and 23 are rejected under 35 U.S.C. 102(b) as being anticipated by Lehmann et al. (Protein Engineering 13(1):49-57, January 2000; cited in the IDS).

22. This rejection, which has been discussed at length in Paper No. 12, mailed on 12/18/2002, was previously applied to canceled claims 1-6 and is now applied to newly added claims 17 and 23 for the reasons of record.

23. Applicants argue that designing an “ancestral protein” is not the same as designing a “consensus protein”. Applicants submit that designing an ancestral protein requires taking into account a phylogenetic tree whereas designing a consensus protein does not. Applicants also submit Table A in support of the argument that while a consensus protein and an ancestral protein may overlap, they are not necessarily the same. Furthermore, Applicants argue that designing a consensus sequence is greatly affected by the

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sequences used whereas designing an ancestral protein is less prone to this bias. It is Applicant's opinion that the Examiner's statement indicating that not all proteins are intended to be functional at high temperatures is irrelevant since Applicant's invention is intended to improve the thermostability of a protein and not to modify a protein such that it can be functional at high temperature. Applicants conclude their arguments indicating that Lehmann et al. does not anticipate the claimed invention since it does not disclose or suggest constructing an ancestral protein and submit that Lehmann et al. does not render the instant invention obvious since it does not teach the differences between designing a consensus protein and an ancestral protein.

24. Applicant's arguments have been fully considered but are not deemed persuasive to overcome the rejection. In regard to Applicant's arguments that the Examiner's statement is not relevant to the instant case, it is noted that the use of the term "high temperature" in the statement was in reference to temperatures which are higher than those which are optimal for maximum activity and did not imply a specific temperature range. As such, the Examiner disagrees with Applicant's contention that the statement is of no relevance since it is not expected that the claimed method can improve the thermostability of any protein of any function as some proteins are not designed to be functional at temperatures which are higher than their optimal temperature. In regard to Applicant's arguments distinguishing between "ancestral protein" and "consensus protein", the Examiner acknowledges Applicant's submission of Table A and Applicant's statements in regard to the differences between a consensus protein and an ancestral protein. However, it is noted that the instant claims do not recite a limitation in regard to the use of a phylogenetic tree in the design of an ancestral protein and the specification does not define an ancestral protein as one which is designed using a phylogenetic tree. Therefore, in the absence of such definition, one of skill in the art would have to use the broadest interpretation of the term, which in the instant case is that of a protein which shares common structural elements with proteins from several different organisms. As indicated in previous Office Action Paper

No. 12, the consensus protein of Lehmann et al. is a protein which is constructed by multiple alignment of 13 phytases from six different fungal species. Furthermore, Lehmann et al. teaches testing and selection of the consensus protein which shows improved thermostability. Therefore, the teachings of Lehmann et al. anticipate claims 17 and 23 as written.

Conclusion

25. No claim is in condition for allowance.
26. Applicant's amendment canceling claims 1-16 and adding claims 17-26 necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

27. Applicants are requested to submit a clean copy of the pending claims (including amendments, if any) in future written communications to aid in the examination of this application.
28. Certain papers related to this application may be submitted to Art Unit 1652 by facsimile transmission. The FAX number is (703) 308-4556. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If Applicant submits a paper by FAX, the original copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Delia M. Ramirez whose telephone number is (703) 306-0288. The examiner can normally be reached on Monday-Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy can be reached on (703) 308-3804. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Delia M. Ramirez, Ph.D.
Patent Examiner
Art Unit 1652

DR

August 21, 2003


REBECCA E. PROUTY
PRIMARY EXAMINER
GROUP 1300
1600